Title: The fatty acid kinase of *Staphylococcus aureus* controls virulence

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Abstract: During previous studies, we identified the fatty acid kinase VfrB as a potent regulator of α-hemolysin and other virulence factors in *Staphylococcus aureus*. Now, we have demonstrated that VfrB is a positive activator of the SaeRS two-component regulatory system. Analysis of mutant strains revealed that VfrB is functioning in the same pathway as SaeRS, leading to transcriptional changes in Sae-dependent genes. This included expression of *saePQRS*, demonstrating a need for this protein in the auto-regulation feedback of SaeRS. The requirement for VfrB-mediated activation is circumvented when SaeS is constitutively active due to an SaeS (L18P) substitution. Furthermore, activation of SaeS via human neutrophil peptide-1 (HNP-1) overcomes the dependency on VfrB for transcription from low-affinity Sae promoters. *In vivo*, the *vfrB* mutant causes enhanced virulence in a murine model of skin infection. Collectively, the studies implicate VfrB as a novel accessory protein needed for activation of SaeRS in *S. aureus*, consequently leading to altered virulence factor production to modulate virulence.